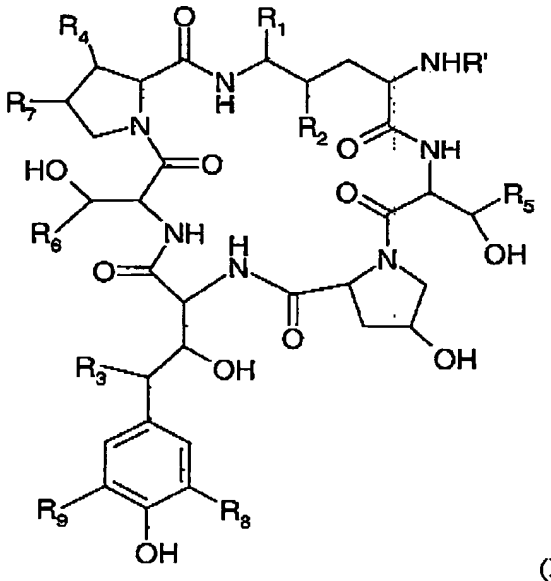
Application Ser. No.: 10/031,764
Filing Date: September 30, 2002
Examiner: Audet, Maury A.

Amendment Pursuant to 37 C.F.R. § 1.121

IN THE CLAIMS:

The claims set forth below with amendments as indicated will replace all prior versions and listing of claims in the application.

1. (currently amended) A compound selected from the group consisting of a cyclohexapeptide compound of the formula (I),



(I)

wherein,

R' is selected from the group consisting of C_9-C_{20} alkyl; C_9-C_{20} alkenyl; C_9-C_{20} alkoxyphenyl, phenyl, biphenyl, terphenyl, and naphthyl; C_1-C_{12} alkylphenyl, C_8-C_{12} alkenylphenyl, C_1-C_{12} alkoxyphenyl; linoleoyl; palmitoyl; 12-methylmyristoyl; 10,12-dimethylmyristoyl; and $COC_6H_4(p)OC_8H_{17}$,

R_1 is selected from the group consisting of -CN; $-CH_2NH_2$; $-N_3$; aryl; substituted aryl; imidazolyl; morpholinoethylamino; -OR, wherein R is ~~C_1-C_{12} alkyl;~~ C_1-C_{12} alkyl, substituted alkyl of $(CH_2)_n$-X, where n is 1-5 and X is selected from the

group consisting of OH, aryl, Cl, Br, I, COOY and CN, wherein Y is selected from the group consisting of C_1-C_6 alkyl, C_2-C_{12} alkenyl, aryl, fused aryl, substituted aryl, a heterocyclic containing 1-3 heteroatoms, mono or di-substituted aminoalkyl and a hydroxy protecting group;

R_3 is selected from the group consisting of –OH; -CN; $-CH_2NH_2$; $-N_3$; aryl; substituted aryl; heterocyclyl and substituted heterocyclyl with 1-3 of heteroatoms; aminoalkylamino; mono or di-substituted linear or cyclic aminoalkylamino; imidazolyl; -OR, wherein R is C_1-C_{12} alkyl; substituted alkyl of $(CH_2)_n$-X, where n is 1-5 and X is selected from the group consisting of OH, aryl, Cl, Br, I, COOY, CN, NH_2 and heterocyclic, wherein Y is selected from the group consisting of C_1-C_6 alkyl, C_2-C_{12} alkenyl, aryl, fused aryl, substituted aryl, a heterocyclic containing 1-3 heteroatoms, mono or di-substituted aminoalkyl, and a hydroxy protecting group;

R_2 and R_4 are independently –H or –OH;

R_5 is –H or $-CH_3$;

R_6 is selected from the group consisting of –H, $-CH_3$ and $-CH_2CONH_2$;

R_7 is selected from the group consisting of –H, $-CH_3$ and –OH;

R_8 and R_9 are independently –H or $-CH_2$-Sec.amine in which the sec.amine is attached to $-CH_2$ through its N linkage; with the proviso that both R_8 and R_9 are not simultaneously hydrogen;
and its non-toxic pharmaceutically acceptable salts.

2. (previously presented) The compound of claim 1 wherein R_1 is OR, and R_3 is selected from the group consisting of –OH, -OR and imidazolyl wherein R in each case is selected from the group consisting of C_1-C_{12} alkyl, substituted alkyl of -$(CH_2)_n$-X, where n is 1-5, X is selected from the group consisting of OH, aryl, Cl, Br, I, COOY and CN, and wherein Y is selected from the group consisting of C_1-C_6 alkyl, -C_2-C_{12}-alkenyl, aryl, fused aryl, substituted aryl, a heteroaryl containing 1-3 heteroatoms, a heterocyclic containing 1-3 heteroatoms, mono or di-substituted aminoalkyl and a hydroxy protecting group.

3. (previously presented) The compound of claim 1 wherein R' is selected from the group consisting of linoleoyl, palmitoyl, 12-methylmyristoyl, 10,12-dimethylmyristoyl and -$COC_6H_4(p)OC_8H_{17}$.

4. (previously presented) The compound of claim 1 wherein 1) to the nitrogen atom of the secondary amine are attached at least one member of the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkenyl, aryl, substituted aryl, alkylaryl and substituted alkylaryl, or 2) the nitrogen atom of the secondary amine is part of a heterocyclic group, optionally substituted by at least one member of the group consisting of C_1-C_6 alkyl, C_1-C_6 alkenyl, aryl, amino, nitro, and halogen, or 3) the nitrogen atom of the secondary amine is part of a fused heterocyclic group, wherein the heterocyclic group contains 1-3 heteroatoms.

5. (previously presented) The compound of claim 1 wherein the secondary amine is selected from the group consisting of piperidine, pyrrolidine, 4-methylpiperidine, morpholine, dimethylamine, diisopropylamine, 4-piperidino-piperidine, piperazine, 1-methylpiperazine, 1-(2-fluorophenyl)piperazine, 1-(2-chlorophenyl)piperazine, 1-(2-pyrimidyl)piperazine, 1-(4-fluorophenyl)piperazine, N-(α,α,α,-trifluoro-m-tolyl)piperazine, 1-phenylpiperazine, 1-benzylpiperazine, 1-(2-pyridyl)piperazine, 1-(4-pyridyl)piperazine, 1-(4-methylphenyl)piperazine,

1-(2,6-dimethylphenyl)piperazine, 1-(1-phenylethyl)piperazine, dibenzylamine, N-(tertbutyl)benzylamine and N-(isopropyl)-benzylamine.

6. (currently amended) The compound of claim 1, wherein R' is 12-methylmyristoyl, R_1 is selected from the group consisting of -CN, $-CH_2NH_2$, $-N_3$, aryl, substituted aryl, $-OCH_2C_6H_4$, $-OCH_3$,$-OCH_2OH$, morpholinoethylamino and imidazolyl R_3 is selected from the group consisting of –OH, -CN, $-CH_2NH_2$, $-N_3$, aryl, substituted aryl, heterocyclyl and substituted heterocyclyl having 1-3 heteroatoms, aminoalkylamino, and mono or di-substituted linear or cyclic aminoalkylamino, R_5 and R_7 are both $-CH_3$, and R_6 is ~~–H, and R_8 and R_9 are both –H~~.

7. (original) An antifungal composition comprising a fungicidally effective amount of a compound of claim 1, and a non-toxic pharmaceutically acceptable carrier.

8. cancelled.

9. (previously presented) A process for the production of a compound of claim 1 comprising:

a) reacting a cyclohexapeptide compound of claim 1, wherein R', R_2, R_4, R_5, R_6 and R_7 are as defined in claim 1, R_1 and R_3 are both –OH, and R_8 and R_9 are –H, with an alcohol in the presence of an acid in an aprotic solvent at a temperature of 0°C to 60°C to obtain the corresponding cyclohexapeptide derivative of claim 1 wherein R', R_2, R_4, R_5, R_6 and R_7 are as defined in claim 1, R_1 and R_3 are independently –OH or –OR wherein at least one of R_1 or R_3 is –OR, R is selected from the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkenyl, fused aryl, substituted aryl, a heterocyclyl containing 1-3 heteroatoms, mono or di-substituted aminoalkyl; and a hydroxy protecting group, and R_8 and R_9 are –H;

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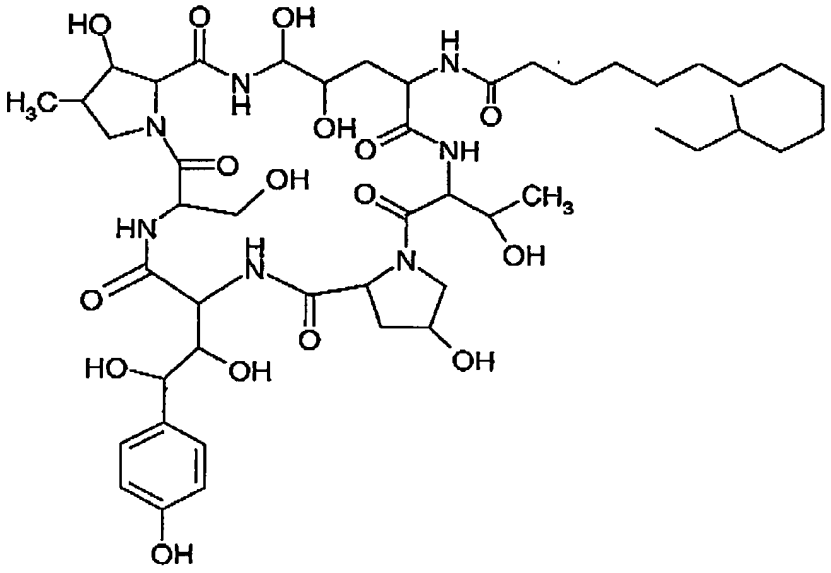
b) reacting the compound of step (a) with a secondary amine in the presence of paraformaldehyde in an aprotic solvent at a temperature of 60°C to 150°C to obtain the desired compound of formula I, isolating and purifying the resulting compound from the reaction mixture in a known manner and optionally converting the compound of formula I into its pharmaceutically acceptable salt in a known manner.

10. (currently amended) A process for the preparation of a cyclohexapeptide compound of claim 1 comprising:

a) reacting mulundocandin of the formula



(IV)

with a nucleophile in the presence of an acid in an aprotic solvent at a temperature of 0°C to 60°C to obtain the corresponding cyclohexapeptide derivative of the formula

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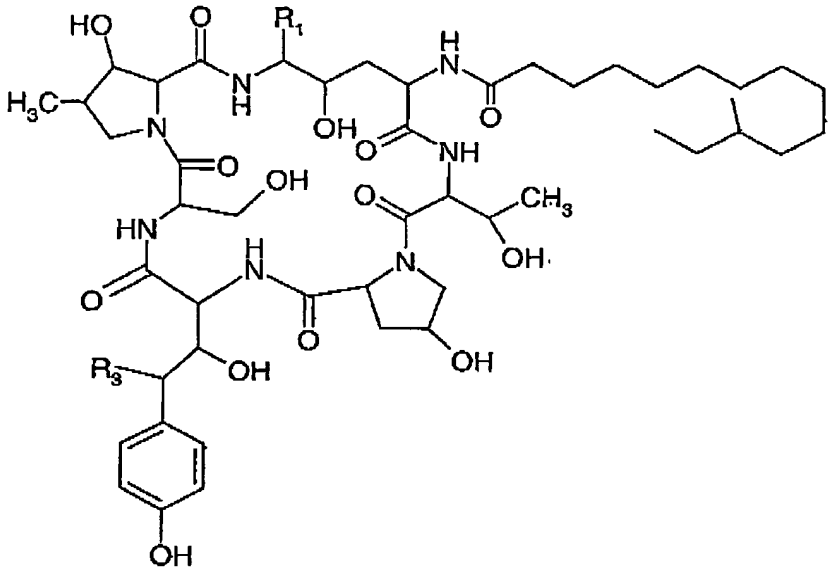

(V)

wherein R_1 and R_3 are –OH or –SR with at least one of R_1 or R_3 is –SR, R is selected from the group consisting of C_1-C_{12} alkyl, substituted alkyl of $-(CH_2)_n$-X, where n is 1-5, X is Cl, Br, I, COOY, CN, NH_2 and a heterocyclic, Y is selected from the group consisting of C_1-C_6 alkyl; C_2-C_{12} alkenyl; aryl; fused aryl; substituted aryl; a heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; and a hydroxy protecting group;

b) reacting the compound of step (a) with an oxidizing agent in an aqueous medium at a temperature of 20°C to 60°C to obtain the corresponding sulfones of formula V wherein R_1 and R_3 are –OH or $-S(O_2)R$, with at least one of R_1 or R_3 is $-SO_2R$, R is selected from the group consisting of C_1-C_{12} alkyl, substituted alkyl of $-(CH_2)_n$-X, where n is 1-5, X is Cl, Br, I, COOY, CN, NH_2 and a heterocyclic, Y is selected from the group consisting of C_1-C_6 alkyl; C_2-C_{12} alkenyl; aryl; fused aryl; substituted aryl; a heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; and a hydroxy protecting group;

c) reacting the sulfone of step(b) with a ~~nucleophile~~ secondary amine in a solvent at a temperature of 20°C to 60°C to obtain the desired compound of claim 1, isolating and purifying the resulting compound and optionally converting the compound of claim 1 into its pharmaceutically acceptable salt in a known manner.